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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte CHARLES A. NICOLETTE

Appeal 2008-2541
Application 10/041,977
Technology Center 1600

Decided: May 29, 2008

Before ERIC GRIMES, LORA M. GREEN, and
RICHARD M. LEBOVITZ, *Administrative Patent Judges*.

GREEN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the Examiner's final rejection of claims 1, 2, 4-18, 20-23, and 25-28. We have jurisdiction under 35 U.S.C. § 6(b). Claim 1 is representative of the claims on appeal, and reads as follows:

1. A method for identifying a cytotoxic T cell epitope comprising the steps in order of:

a) contacting a population of at least two cytotoxic T cells having the same MHC-haplotype restriction with a quantity of molecule released from a solid phase support, wherein said solid phase support is present in

i) a library of molecules, which molecules are attached to a plurality of solid phase supports by a releasable linker, each of said solid phase supports comprising a plurality of identical copies of a single species of molecule, and wherein the structure of the molecule is determinable, which library of molecules contains a conserved structural motif corresponding to a structural motif characteristic of peptides that associate with the MHC-haplotype to which the cytotoxic T cells are restricted; wherein said quantity of released molecule consists of an amount less than the plurality of said single species of molecule attached to said solid support; and

ii) antigen presentation means, which antigen presentation means correspond to the MHC-haplotype to which the cytotoxic T cells are restricted;

wherein the solid phase supports of the library are in separate fractions;

b) detecting cytotoxic T cell activation effected by the formation of a complex of a cytotoxic T cell, a single species of released molecule, and said antigen presentation means; and

c) determining the structure of said molecule.

The Examiner relies on the following references:

Lam	5,510,240	Apr. 23, 1996
Melief	5,554,724	Sept. 10, 1996

Van der Zee, et al., "Efficient mapping and characterization of a T Cell epitope by the simultaneous synthesis of multiple peptides," *Eur. J. Immunol.*, Vol. 19, pp. 43-47 (1989)

Engelhard, "Structure of peptides associated with MHC class I molecules," *Curr Opinion in Immunol.*, Vol. 6, pp. 13-23 (1994)

We affirm.

DISCUSSION

Claims 1, 2, 4-7, 9-17, 20-23, and 25-28 stand rejected under 35 U.S.C. § 103(a) as being obvious over the combination of Van der Zee and Lam. As Appellant does not argue the claims separately, we focus our analysis on claim 1, and claims 2, 4-7, 9-17, 20-23, and 25-28 stand or fall with claim 1. 37 C.F.R. § 41.37(c)(1)(vii).

Van der Zee is relied upon for teaching "a method for efficient mapping and characterization of a T cell epitope by the simultaneous synthesis of multiple peptides." (Ans. 3.) According to the Examiner, in the original Pepscan method, "small amounts of several hundreds of peptides are synthesized on activated polyethylene rods (solid supports of the instant claims) and then arrayed in a micro titer plate; after synthesis and deprotection the peptides, (referring to the library of molecules attached to solid phase supports), remain attached to the rods for subsequent analysis of their reactivity with antibodies, (i.e., B cell receptors)." (*Id.*)

For the characterization of T cell epitopes, Van der Zee is cited for teaching that the peptides must be detached from the solid support for the screening assay (*id.*). Van der Zee teaches that T cell clones A2b and A2c are used in a T cell stimulatory assay, in which the T cells are incubated with peptides that have been released from a solid support (as taught by Van der Zee, a rod), in the presence of syngeneic thymocytes as the antigen presenting cells (APCs), in which T cell stimulation is measured by monitoring ^{3}H-thymidine incorporation (Ans. 3-4). The Examiner notes further that Van der Zee "also discloses that the sequence of the epitope peptides is determined; substituted peptides are prepared by single amino acid substitutions, insertions and deletions; and the analogs of the peptides

are tested for activity using the same T cell clones," and that "the Pepscan method was also used to prepare a large number of epitope analogs having replacements, deletions, insertions of the residue in a nonapeptide that contain the epitope." (*Id.* at 4.) Thus, according to the Examiner, Van der Zee determined the essential residues of the T cell epitope by synthesis and testing of variants (*id.*).

Van der Zee, the Examiner notes, does not teach cleaving only a portion of the linkers such that a only a portion of the molecule attached to a bead is released (Ans. 4).

Lam is cited for teaching a method of screening a peptide library in which peptides are synthesized on solid phase supports using selectively cleavable linkers (*i.e.*, the releasable linkers) to allow sequential cleaving of the peptides from a single bead (Ans. 4). In testing for a desired biological activity, beads from wells demonstrating biological activity are isolated and the bio-oligomer that has remained attached to the bead is sequenced (*id.* at 5). Lam is also relied upon for teaching that "in the disclosed screening method only a small number of beads are removed during each screening step, the majority of the beads remain in the pool, and therefore the random bio-oligomer can be reused multiple times." (*Id.*)

The Examiner concludes that

> it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use selectively cleavable linkers to attach peptides to beads, as taught by Lam [ ], in combination with the method of Van der Zee [ ], with the expectation of identifying T cell epitopes from the library and synthesizing variants of the epitope. Because Lam [ ] teach[es] the advantages of the use of cleavable linkers, such that only a fraction of peptides are cleaved from the beads, so as to identify the T cell epitopes, as taught by Van der Zee [ ]; and then still

> to have peptides attached to the beads, which would be useful in structure analysis methods. Van der Zee [ ] teach[es] methods of synthesis of T cell epitopes on solid phase supports and methods for identifying the T cell epitope using T cell clones and APC. Van der Zee [ ] teach[es] sequencing the positive peptides from the library and making new variant peptides using the sequence data of the positive peptides. These variants were then tested for T cell stimulation. Thus, one skilled in the art at the time the invention was made, would have been motivated to use the methods of Lam [ ], in the methods of Van der Zee with the expectation of identifying T cell epitopes and determining the structure of the epitopes and to use the information in the synthesis of T cell epitope variants which would be useful as therapeutics or in diagnosis.

(*Id.* at 5-6.)

"In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a prima facie case of obviousness. Only if that burden is met, does the burden of coming forward with evidence or argument shift to the applicant." *In re Rijckaert*, 9 F.3d 1531, 1532 (Fed. Cir. 1993) (citations omitted). The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) secondary considerations of nonobviousness, if any. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). The Supreme Court has recently emphasized that "the [obviousness] analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR Int'l v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007). "The combination of familiar elements according to known methods

is likely to be obvious when it does no more than yield predictable results." *Id.* at 1739. Moreover, an "[e]xpress suggestion to substitute one equivalent for another need not be present to render such substitution obvious." *In re Fout*, 675 F.2d 297, 301 (CCPA 1982). As we conclude that the Examiner has set forth a prima facie case of obviousness as to claim 1, we turn to Appellant's arguments in rebuttal.

Appellant argues that the Examiner did not consider the claimed invention as a whole (App. Br. 8.) Specifically, Appellant argues that "[n]o reference to a critical limitation of the instant invention, wherein each of the assay components is correlated for MHC-haplotype status and including the use of peptide libraries based upon MHC-haplotype status of the population of cytotoxic T cells to be tested, appears in the rejections." (*Id.*) Thus, according to Appellant, "Van der Zee does not teach the use of T cells, oligopeptides and antigen presenting means, each of which correspond to the same MHC-haplotype restriction." (*Id.* at 12.) Appellant argues that Van der Zee relies on syngeneic thymocytes as antigen presenting means, therefore "it would not be necessary for Van der Zee to correlate the MHC status of the cytotoxic T cells, the oligopeptides and the antigen presentation means." (*Id.* at 13.)

Van der Zee teaches assay of the T cell clones, A2b and A2c , which recognize a mycobacterial epitope that displays antigenic mimicry with a cartilage-associated molecule (Van der Zee, p. 44, first column). The A2b clone induces arthritis after *in vivo* inoculation in syngeneic Lewis rats, whereas the A2c clone protects Lewis rats against arthritis by subsequent challenge with mycobacteria (*id.*). Thus, the clones A2b and A2c read on at least two cytotoxic T cells having the same MHC-haplotype restriction. We

note that we could not find a specific definition of "MHC-haplotype restriction" in the Specification that would conflict with that finding, nor does Appellant provide one.

In addition, Van der Zee teaches the synthesis of a library of overlapping nonapeptides corresponding to residues 170-205 of the 65 kDa mycobacterial protein (Van der Zee, p. 45, Table 2). Based on the ability of the peptide to induce a full T cell response, a second library was synthesized based on a nonapeptide that was essential for stimulation of A2b and A2c, which library contained substitutions, insertions, and deletions (*id.* at 46, first column). Those libraries read on a library of molecules containing a conserved structural motif corresponding to a structural motif characteristic of peptides that associate with the MHC-haplotype to which the cytotoxic T cells are restricted.

Finally, Van der Zee teaches assaying for stimulatory activity using syngeneic thymocytes as the antigen presenting cells (*id.* at 44, second column). Such cells read on antigen presentation means corresponding to the MHC-haplotype to which the cytotoxic T cells are restricted. Just because it would not be necessary for Van der Zee to correlate the MHC status of the cytotoxic T cells, the oligopeptides and the antigen presentation mean because of the use of the syngeneic cells, does not mean that the use of syngeneic cells does not meet that limitation.

Thus, although Van der Zee does not specifically discuss matching the assay components to MHC-haplotype status, the reagents of Van der Zee appear to meet that limitation.

Appellant also argues that, "prior to the present invention, it was not appreciated that one would be able to meaningfully detect T cell activation

when more than one peptide species having the requisite MHC-haplotype was released and evaluated in a single ('competitive') assay along with other released peptide species," and Van der Zee does not teach or suggest such a competitive evaluation (*id.* at 14).

Appellant's argument has been considered, but it is not commensurate in scope with the subject matter of claim 1, which does not require the use of competitive evaluation nor for more than one released peptide to be evaluated, as claim 1 recites that the solid phase supports of the library are in separate fractions.

Appellant argues that Van der Zee "does not teach detecting cytotoxic T cell activation by evaluating lysis of the antigen presentation means by the activated cytotoxic T cells." (App. Br. 14.) Van der Zee, Appellant asserts, relies on the use of a T cell stimulatory or proliferation assay (*id.*).

Appellant's argument is not commensurate in scope with the claimed subject matter. Claim 1 requires the step of "detecting cytotoxic T cell activation effected by the formation of a complex of a cytotoxic T cell, a single species of released molecule, and said antigen presentation means." Thus, there is nothing in claim 1 that requires detecting T cell activation by cell lysis. Moreover, the Specification teaches that cytotoxic T cell activation can be evaluated by detecting ^{3}H-thymidine incorporation, which is the same method used by Van der Zee (Van der Zee, p. 44, second column (T cell stimulatory activity)).

Appellant argues further that the Examiner engaged in impermissible hindsight in combining the references (App. Br. 8). According to the Appellant, the rejections "clearly lack a specific, motivating rationale or principle," but instead are "non-specific and unsupported." (*Id.* at 9.)

Appellant asserts that Van der Zee already teaches a method of cleaving the peptides from the support, and wonders "why an artisan would seek an alternative cleavage method where a known, successful method was provided within the reference." (*Id.*) In addition, Appellant argues that Van der Zee also states that the quantity cleaved from the supports was adequate and left peptide on the support for further analysis, thus there is no motivation to combine Lam with Van der Zee (*id.* at 10).

Appellant's arguments have been considered, but are not convincing. If we were to accept the arguments at face value, there would be no need for an obviousness analysis, as most, if not all, obviousness rejections are based on a reference that uses something that already works.

Moreover, as to motivation to combine, the Supreme Court in *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1739 (2007), rejected a rigid application of the teaching-suggestion-motivation test. The Court recognized that it is often necessary to look at the interrelated teachings of multiple references; the effects of demands of the marketplace; and the background knowledge possessed by a person of ordinary skill, "all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed." *Id.* at 1740-41. Moreover, the "obviousness analysis cannot be confined by a formalistic conception of the words teaching, suggestion, or motivation, or by overemphasis on the importance of published articles and explicit content of issued patents." *Id.* at 1741.

> If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability. For the same reason, if a technique has been used to improve one device, and a person of ordinary skill would recognize that it would

> improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill.

Id. at 1740. Although the Court speaks in terms of devices, the reasoning is equally applicable to methods, such as the method of claim 1. In this case, the ordinary artisan would understand that the libraries and cleavable linkers of Lam could be used in the T cell screening method of Van der Zee, as Van der Zee teaches that the peptides must be detached from the solid supports in order to interact with the T cells, and Lam teaches peptide libraries that are selectively cleavable from a solid support.

Appellant asserts further that Van der Zee teaches away from the combination (App. Br. 10). First, according to Appellant, none of the derivatives were "significantly superior to the native epitope," thus "other than for mapping or characterization of a known T cell epitope, one skilled in the art would not be motivated to prepare or analyze derivative epitopes." (*Id.*) Second, Appellant argues, Van der Zee would not encourage one skilled in the art to expend time and resources to search for non-native epitopes, as all the derivatives tested by Van der Zee were based on the known native sequence, and the native epitope would be used with only one change per peptide (*id.* at 11). Appellant asserts that the instant invention is drawn to "seeking a method to identify a wide range of 'derivatized natural epitopes' (i.e., non-natural or altered ligands)," as "non-native ligands offer improved immunological reactivity." (*Id.*)

"Under the proper legal standard, a reference will teach away when it suggests that the developments flowing from its disclosures are unlikely to produce the objective of applicant's invention. A statement that a particular combination is not a preferred embodiment does not teach away absent clear

discouragement of that combination." *Syntex (USA) LLC v. Apotex, Inc.*, 407 F.3d 1371, 1380 (Fed. Cir. 2005) (citations deleted). We find that none of the teachings of Van der Zee purported by Appellant to be a teaching away in fact meet the standard of a teaching away. We thus conclude that the Examiner properly combined Van der Zee with Lam to arrive at the method of claim 1. Moreover, many of Appellant's arguments, such as that the instant invention is drawn to "seeking a method to identify a wide range of 'derivatized natural epitopes' (i.e., non-natural or altered ligands)" (App. Br. 11), are not commensurate in scope with method of claim 1, as there is nothing in claim 1 requiring the use of libraries limited to derivatized natural epitopes.

Finally, Appellant argues, there must be a reasonable expectation of success, and no such expectation is provided by the combination as the cited references fail to teach and/or suggest all of the elements of the claimed invention (App. Br. 15). But for the reasons set forth above, we find that the combination does teach and/or suggest all of the elements of the method of claim 1, and thus there is a reasonable expectation of success of using the libraries of Lam in the T cell assay method of Van der Zee. The rejection is thus affirmed as to claim 1, and as claims 2, 4-7, 9-17, 20-23, and 25-28 stand or fall with claim 1, the rejection is affirmed as to those claims as well.

Claims 1, 2, 4-17, 20-23, and 25-28 stand rejected under 35 U.S.C. § 103(a) as being obvious over the combination of Van der Zee and Lam as further combined with Engelhard. In addition, claims 1, 2, 4-7, 9-18, 20-23, and 25-28 stand rejected under 35 U.S.C. § 103(a) as being obvious over the combination of Van der Zee and Lam as further combined with Melief.

As Appellant does not argue these rejection separately, and as we have already affirmed the rejection of claims 1, 2, 4-7, 9-17, 20-23, and 25-28 under 35 U.S.C. § 103(a) as being obvious over the combination of Van der Zee and Lam, these rejections are also affirmed.

CONCLUSION

In summary, we conclude that the Examiner has set forth a prima facie case of obviousness as to all of the claims on Appeal, and we thus affirm the rejection of 1, 2, 4-7, 9-17, 20-23, and 25-28 under 35 U.S.C. § 103(a) as being obvious over the combination of Van der Zee and Lam; the rejection of claims 1, 2, 4-17, 20-23, and 25-28 under 35 U.S.C. § 103(a) as being obvious over the combination of Van der Zee and Lam as further combined with Engelhard; and the rejection of claims 1, 2, 4-7, 9-18, 20-23, and 25-28 under 35 U.S.C. § 103(a) as being obvious over the combination of Van der Zee and Lam as further combined with Melief.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

dm

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